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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|-------------------------|------------------|
| 09/300,425 | 04/28/1999 | DARIO NERI | 113000.301 | 4446 |
| 23599 | 7590 | 01/25/2005 | EXAMINER | |
| MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201 | | | PORTNER, VIRGINIA ALLEN | |
| | | ART UNIT | PAPER NUMBER | |
| | | 1645 | | |

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/300,425 | NERI ET AL. | |
| | Examiner | Art Unit | |
| | Ginny Portner | 1645 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 18 October 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 14-17,20-24,28-35 and 37-45 is/are pending in the application.
- 4a) Of the above claim(s) 14-17,19,25-27,36 and 46-50 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 20-24,28-35 and 37-45 is/are rejected.
- 7) Claim(s) 35 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Claims 14-17, 19-50 are pending.

Claims 14-17, 19, 25-27, 36, 46-48 and 49-50 are herein withdrawn from consideration.

Claims 20-24, 28-35, 37, 38, 39-45 have been amended to recite new claim limitations, and are under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

1. Newly submitted claims 49-50 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 49 and 50 depend from claims 16-17 which were non-elected claims, not examined in the instant Application, therefore, claims 49-50 also are herein withdrawn from consideration as being directed to a non-elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 49-50 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

2. Newly submitted claims 36 and 46-48 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 36 has been newly amended to recite a combination of limitations that defines a species of invention not previously considered on the record. SEQ ID No 30 is a sequence of 4 amino acids and the newly claimed variable VH domain is recited to comprise mutations at locations not contained

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in SEQ ID NO 30; never the less, the combination of mutations of SEQ ID NO 30 together with mutations in SEQ ID NO 32 of the Instant Specification have not previously been considered on the record and therefore is directed to an independent and distinct invention defined by a combination of mutations in two specific Seq ID Nos not previously searched nor considered.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 36 and 46-48 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejections Withdrawn

3. Claims 20-23, 33-35 rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al (WO97/45544) is herein withdrawn in light of the amendment of the claims to recite the phrase less than 54 pM which is a range not specifically taught by the prior art.
4. Claims 20-24, 28-37 and 39 rejected under 35 U.S.C. 103(a) as being unpatentable over Neri in view of Theodore is herein withdrawn in light of the amendment of the claims to recite less than 54 pM which is a range not specifically taught by the prior art.
5. The title is now descriptive of the claimed invention.
6. Claim 20 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reciting the relative term “high affinity” has been obviated by the amendment of the claim to recite a specific affinity (Kd).

7. Claim 35 rejected for reciting “CDR” is no longer unclear as this term now is accompanied with the term “regions”, and no longer be in question as to whether they were specific amino acids or a region.

8. Claim 36 rejected for reciting “VL” and “VH” is no longer unclear as this term is accompanied with the term “the VH domain” and “the VL domain”, and are no longer be in question as to whether the claim recited specific amino acids or a region.

Rejections Maintained

9. The Brief Description of the Drawings has not been amended to clearly, but briefly describe the images set forth in the drawings (see paragraph 7, paper number 5132004).

10. The Specification is still objected to for informalities at page 14, lines 13-20, and Table 1, page 27, for reasons set forth in paper number 5132004, paragraph 13.

11. Claim 35 rejected under 35 USC, 112, second paragraph for not defining the type of mutations, number or location of the mutations; no upper limit is recited as the claim has been amended to recite the phrase “at least one” and previously recited “a limited number”, but what these mutations are, or how many is still unclear.

12. Claim 36 rejected under 35 USC 112, second paragraph for not reciting a reference sequence is maintained in light of the fact that SEQ ID Nos 30 and 32 only contain 4 amino acids and 6 amino acids respectively, and the claims are directed to sequences that contain up to 54 and 50 amino acids respectively. The claim is still unclear. Please see the sequence listing in the instant Application for the number of amino acids set forth in SEQ ID NO 30 and 32.

Response to Arguments

13. Applicant's arguments with respect to claims 20-24, 28-35, 37, 38, 39-45 have been considered but are moot in view of the new ground(s) of rejection.

Specification

14. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. At page 10, lines 29 and 31, hyperlinks are embedded in the instant Specification which must be removed.

15. **Please Note:** The amendment of the instant Specification submitted September 1, 2000, directing the insertion of SEQ ID Nos into the Specification at page 27 was not entered as the SEQ ID No were considered to be too extensive to enter. The new page 27 for substitution into the instant Specification that was mentioned in Applicant's remarks was not received. Resubmission of this amendment is requested.

Double Patenting

16. Claim 20 of this application is in conflict with claims 12-13 of Application No. 10/321,558. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Objections

17. Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.
18. Claim 35 has been amended to recite the phrase “at least one mutation in one or more residues of its CDR regions, which increases the affinity of the antibody for ED-B domain”. The Kd value of claim 35 is not limited to the recited range of Kd values defined in claim 20 from which claim 35 indirectly depends through claim 33, therefore claim 35 broadens the scope of the claims from which it depends.

Claim Rejections - 35 USC § 112

19. Claims 20-24, 28-35,37-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

All of the claims under consideration either directly or indirectly depend from claim 20 which has been amended to recite the phrase “less than about 54 pM”. The examiner upon reconsideration of the disclosure provided by the Instant Specification to define the claimed invention found at page 17, line 26 the Kd of antibody L19 defined to be “L19=54pM”. Original descriptive support for the newly submitted range of Kd binding affinities could not be

found in the instant specification. The binding specificity of antibody "L19" was defined to be equal to 54 pM and not "less than about 54pM". While the recited range of Kd values encompasses 54pM, which evidences original descriptive support at page 17 of the instant Specification, the newly submitted broad range of Kd values does NOT evidence original descriptive support in the instant Specification. The claimed range of Kd values less than 54 pM are not supported by the disclosure in the instant specification, nor is a range that is about 54 pM supported by the instant Specification provided. While one of the originally submitted claims recited the range 27-54 Kd , the smaller range of about 54 Kd was not found, nor was the range of 50-54 Kd found to be supported by the instant Specification. Additionally, claim 39 has been amended to recite the range 50-54 pM; this range does not evidence original descriptive support in the instant Specification, nor does the phrase "about 54 pM" recited in claim 37. Therefore, the newly submitted amendments to claims 20, and 39, from which all other pending claims which directly or indirectly depend therefore recite New Matter.

Newly amended claim 35, and new claims 43-45 which depend therefrom have been amended to recite the phrase "at least one mutation in one or more residues of its CDR regions", and "the number of mutations" is 1-3, 2 and 1, respectively. The phrase "at least one" recited in claim 35 includes any number of mutations at any position or location in the CDR regions. Additionally, the phrase "a limited number" and "at least one" does not provide original descriptive support for specific numbers of mutations as recited in new claims 43-45. Upon consideration of the originally submitted claims and the disclosure provided by the instant Specification, the examiner found support for mutations at positions 31,32,33, 50,52,54, and 91-98 of the VH chain and positions 32. 50 and 91-96 of the VL domain based upon the definitions

provided in Table 1, on page 27 and original claim 7. No other mutation locations or additional mutations evidence original descriptive support in the instant Specification . The newly submitted combination of claim limitations require the conjugate antibodies to include mutations at any (claims 43-45) position or every position (claim 35) of the CDR regions; these compositions does not evidence original descriptive support in the instant Specification. Claims 35 and new claims 43-45 contain New Matter.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Pat. 6,093,399 and US Pat. 6,7498653 are cited to show compositions and

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methods that utilize an antibody directed to the tumor associated fibronectin isoform which is defined to be onocfetal fibronectin (see claim 47 and 16, respectively).

22. Sekiguchi, K et al (1992) is cited to show monoclonal antibodies to the ED-B domain of fibronectin raised to a recombinant peptide that contained the isolated ED-B domain (see English translation)

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
January 13, 2005

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